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Effects of Blood Pressure Lowering on Cerebral White Matter Hyperintensities in Patients With Stroke

The PROGRESS (Perindopril Protection Against Recurrent Stroke Study) Magnetic Resonance Imaging Substudy

Carole Dufouil, PhD; John Chalmers, MD, PhD; Oguzhan Coskun, MD; Véronique Besançon, MD; Marie-Germaine Bousser, MD; Pierre Guillon, PhD; Stephen MacMahon, PhD; Bernard Mazoyer, MD, PhD; Bruce Neal, MD, PhD; Mark Woodward, PhD; Nathalie Tzourio-Mazoyer, MD, PhD; Christophe Tzourio, MD, PhD; for the PROGRESS MRI Substudy Investigators

Background—The prevalence of white matter hyperintensities (WMHs) detected on cerebral MRI is associated with hypertension, but it is not known whether blood pressure lowering can arrest their progression. We report here the results of an MRI substudy of PROGRESS (Perindopril Protection Against Recurrent Stroke Study), a randomized trial of blood pressure lowering in subjects with cerebrovascular disease.

Methods and Results—The substudy comprised 192 participants who had a cerebral MRI both at baseline and after a mean follow-up time of 36 months (SD=6.0 months). At the first MRI, WMHs were graded with a visual rating scale from A (no WMH) to D (severe WMH). Participants were assigned to a combination of perindopril plus indapamide (or their placebos; 58%) or to single therapy with perindopril (or placebo). At the time of the second MRI, the blood pressure reduction in the active arm compared with the placebo arm was 11.2 mm Hg for systolic blood pressure and 4.3 mm Hg for diastolic blood pressure. Twenty-four subjects (12.5%) developed new WMHs at follow-up. The risk of new WMH was reduced by 43% (95% CI –7% to 89%) in the active treatment group compared with the placebo group ($P=0.17$). The mean total volume of new WMHs was significantly reduced in the active treatment group (0.4 mm^3 [SE=0.8]) compared with the placebo group (2.0 mm^3 [SE=0.7]; $P=0.012$). This difference was greatest for patients with severe WMH at entry, 0.0 mm^3 (SE=0) in the active treatment group versus 7.6 mm^3 (SE=1.0) in the placebo group ($P<0.0001$).

Conclusions—These results indicate that an active blood pressure-lowering regimen stopped or delayed the progression of WMHs in patients with cerebrovascular disease. (*Circulation*. 2005;112:1644-1650.)

Key Words: stroke ■ cerebrovascular disorders ■ magnetic resonance imaging ■ hypertension ■ trials

White matter hyperintensities (WMHs) are often observed on brain MRIs in elderly persons^{1–5} and in patients with stroke.^{6–8} WMHs, which include areas of demyelination as well as silent infarcts, are associated with cognitive impairment or dementia,^{4,9–13} depression,^{14–16} and gait disturbances.^{17,18} Apart from age, the main risk factors for WMHs are vascular, particularly high blood pressure.^{1,2,4} Cross-sectional population-based MRI studies have shown a positive linear relationship between blood pressure and severity of WMHs.^{5,19} From these studies, it also appears that people with uncontrolled hypertension have a higher prevalence of severe WMH than people without hypertension or with controlled hypertension.

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MRI follow-up studies have shown that the total load of WMHs may increase over time but will never decrease.^{17,20,21} To date, it is not known whether it is possible to stop or delay this progression. Because of the strong relationship between blood pressure and WMH, it seems plausible that lowering blood pressure would reduce the incidence of WMHs, although this has never been demonstrated.⁸ To test this hypothesis, we conducted the first MRI-based assessment of WMHs in a substudy of a randomized trial of blood pressure lowering in patients with a history of cerebrovascular disease, the Perindopril Protection Against Recurrent Stroke Study (PROGRESS).²²

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Methods

Study Design and Participants

The design of the PROGRESS study has been described in detail elsewhere.²² Briefly, 6105 participants were recruited from 172 collaborating centers in 10 countries between May 1995 and November 1997. Participants were eligible if they had a history of cerebrovascular disease (stroke or transient ischemic attack but not subarachnoid hemorrhage) within the previous 5 years. In addition, participants were required to have no clear indication for (such as heart failure) or contraindication to treatment with an ACE inhibitor. Active treatment comprised a flexible treatment regimen based on perindopril (4 mg daily), with the addition of indapamide (2.5 mg daily, or 2 mg daily in Japan) in those participants for whom the responsible study physician believed that there was no specific indication for nor contraindication to the use of a diuretic. Those participants assigned placebo received tablets identical in appearance to the active agents. The rationale for the use of combination therapy (perindopril and indapamide or double placebo) rather than single-drug therapy (perindopril or single placebo), wherever possible, was to optimize the fall in blood pressure.

The cerebral MRI substudy was initiated in France in 1995. The St. Antoine ethical committee approved the study, and all patients signed an informed consent. The exclusion criteria included the usual contraindications for MRI, such as prosthetic valves, pacemakers, cerebral aneurysm clips, and a history of intraocular metal fragments, cochlear implants, or claustrophobia. To be eligible, a center needed to have a MRI scanner available and to be able to export the native data. Ten centers were eligible and agreed to participate. Of the 322 patients (159 in the placebo group, 163 in the active treatment group) randomized in these 10 centers, 281 (87%) volunteered to participate (141 in the placebo group, 140 in the active treatment group), but of these, 9 died before their MRI appointment and 18 met 1 of the exclusion criteria (Figure 1). The remaining 254 patients (131 in the placebo group and 123 in the active treatment group) had their first MRI within 6 months of randomization. Among these patients, 29 examinations could not enter the image-processing phase because of low quality, and hence, the final sample included 225 patients (116 in the placebo group and 109 in the active treatment group). The patients randomized who did not participate in the MRI substudy ($n=97$) were older (mean age 64.0 years [$SD=11.0$] versus 60.4 [$SD=10.8$], $P=0.007$) and were more often women (37.5% versus 22.1%, $P=0.004$) than those who participated. These 2 groups did not differ significantly for treatment allocation (44.2% of those who did not participate were assigned to placebo versus 51.6% of those who participated, $P=0.23$) or for hypertension at baseline (59.6% versus 50.9%, $P=0.14$). Similar differences were observed when the group of 192 patients who had both MRI examinations was compared with the 130 patients who did not.

A second MRI examination was scheduled to be performed before the end of the follow-up, on average 3 years after the initial scan (range of 24 to 49 months). Follow-up rate was 86% ($n=192$). Among the 33 patients who did not have a follow-up scan, 14 refused, 13 met 1 of the exclusion criteria, and 6 had died (Figure 1). Subjects who did not have a follow-up MRI ($n=33$) were on average older (mean age 68.9 years [$SD=9.0$] versus 59.0 years [$SD=10.4$], $P<0.001$) and had more frequent severe cerebral WMH on first MRI (48.5% versus 14.0% respectively, $P<0.001$) than subjects who had a follow-up MRI ($n=192$). Gender distribution, baseline blood pressure levels, and intake of antihypertensive medication were similar in both groups. The follow-up rate was slightly higher for those who were in the placebo group (89%) than for those who were in the active treatment group (82%), but the difference was not significant ($P=0.14$). At each step of the study, the rates of refusals or dropouts did not differ significantly between the active treatment and placebo groups.

Magnetic Resonance Imaging

Baseline cerebral MRI was performed with 1.0-Tesla scanners in 5 centers and 1.5-Tesla scanners in 5 other centers. The following procedures were implemented after visits of the MRI coordinating

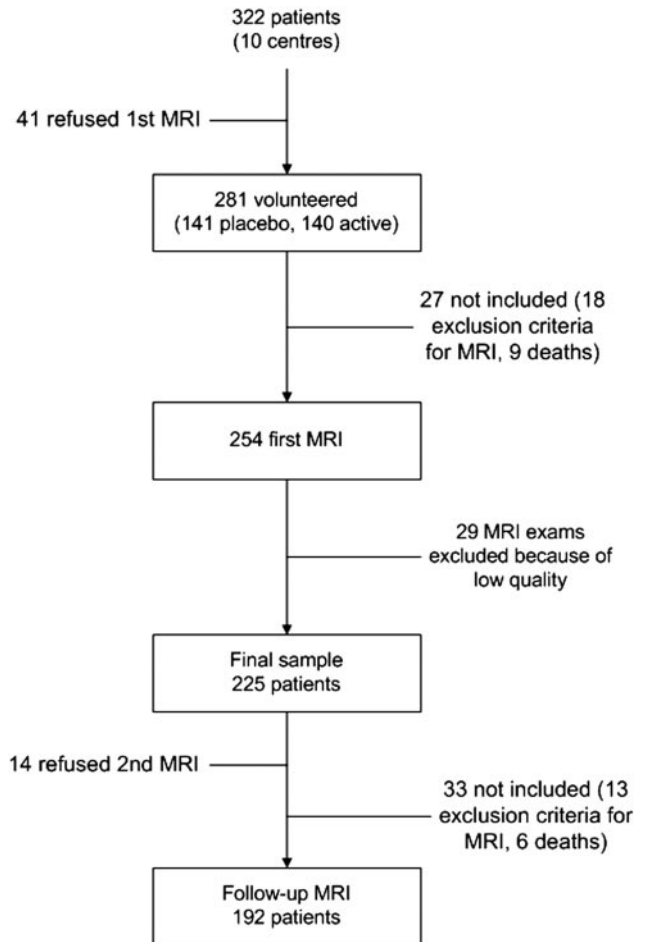


Figure 1. Flowchart of participants in the PROGRESS MRI substudy.

team in each center. For each subject, the orbitomeatal line served as the reference line for brain positioning in the field of view, to ensure maximum field homogeneity over the volume of interest. A paramedial sagittal, T1-weighted thick slice was first acquired to delimit the length of the field of view in the z-axis. A high-resolution, T1-weighted brain volume was subsequently acquired with a 3D, fast spoiled gradient echo sequence (3D-FSPGR, 128 1.4-mm-thick slices, 256×256 matrix, 0.9×0.9 mm² pixel, 24-cm transversal field of view). Proton-density/T2-weighted images were obtained with a fast multislice double-echo 2D axial acquisition (repetition time 3500 ms, time of echo 1=85 ms, time of echo 2=140 ms, 5-mm-thick contiguous slices, 256×256 matrix, 0.9×0.9 mm² pixel, 24-cm transversal field of view). Image-acquisition parameters were identical for both the initial and follow-up MRI examinations.

Because the major goal of the present study was to assess on the follow-up MRI examination the evolution of WMHs, a special procedure had to be implemented to ensure that image interpretation conditions were as similar as possible for both examinations in a given subject. The steps of this procedure were as follows: (1) The follow-up T2 volume was first aligned to the initial one with the automatic image registration algorithm.²³ (2) Histogram equalization was then applied to the 2 T2 volumes, thereby ensuring comparable image characteristics in terms of signal intensity. (3) Finally, a PC-based, user-friendly graphic interface was developed to allow the radiologist to visualize side by side the slices of both the initial and follow-up MRI examinations (Figure 2).



Figure 2. Illustration of the technique used for MRI assessment. On the left side of the Figure, there is an axial T2-weighted image of first MRI examination of a PROGRESS patient. On the right side, the image is taken from the second examination performed at the end of the follow-up. With registration techniques and histogram equalization, it was possible to make this second examination as similar as possible to the first examination, as seen in the Figure, thus facilitating the comparison between the 2 examinations by the neuroradiologist. Despite the small loss of resolution in the second examination due to the technique, it is possible to visualize new lesions close to the left occipital horn.

WMH Assessment

A trained neuroradiologist (OC) blinded to clinical data and treatment allocation established all the ratings. At first MRI examination, the magnetic resonance images were rated visually with respect to the presence of WMH with a modified version of a validated scale.^{5,24} This scale provided an overall WMH grade ranging from A to D, as follows: A, no lesion; B (mild WMH), deep WMH ≤ 3 mm or periventricular hyperintensities ≤ 5 mm; C (moderate WMH), 1 to 10 deep WMHs (4 to 10 mm) or periventricular hyperintensities (6 to 10 mm); and D (severe WMH), more than 10 deep WMHs (4 to 10 mm) or confluent deep WMHs or periventricular hyperintensities ≥ 11 mm. Because of the limited number of subjects, in some analyses we combined categories B and C and used a 3-level grading scale. Comparing baseline and follow-up scans on the same screen, the radiologist also determined the presence of each new WMH that occurred during follow-up, the volume of which was assessed after individual delimitation of the WMH on the computer screen. Volume of incident WMHs was calculated by summing the surfaces of the WMHs on consecutive T2-weighted images, and the slice thickness was used as a third dimension. The presence of prevalent stroke scars was rated by size (small, medium, or large). Stroke scars limited to the white matter were distinguished from WMHs, because they were hypointense on T1-weighted images. Volume of stroke scars was not included in the calculation of volume of prevalent or incident WMH.

Statistical Analysis

All randomized participants who had 2 MRI examinations ($n=192$) were included in the analysis. For baseline comparisons, we used simple χ^2 tests for categorical variables and ANOVA for continuous variables.

We performed logistic regression to assess the relationship between treatment and presence of incident WMH at second MRI. We conducted ANCOVA to compare the total volume of incident WMHs between the active treatment and placebo groups. For both logistic regression and ANCOVA, the initial analyses included adjustment for age, sex, and center. Further adjustments were made for height, stroke type, baseline blood pressure level, antihypertensive treatment intake, interval (in months) between the 2 MRI scans, and baseline severity of WMH. To test the hypothesis that the baseline severity of WMH may modify the relationship between treatment allocation and total volume of incident WMH, we added

TABLE 1. Baseline Characteristics of the PROGRESS MRI Study Participants

	Placebo (n=103)	Active (n=89)	P*
Mean age, y (SD)	60.7 (12.2)	60.9 (12.1)	0.89
Male gender, %	77	75	0.67
Age at highest level of education, y (SD)	17.6 (5.9)	17.2 (4.5)	0.56
Mean height, cm (SD)	170.3 (9.0)	168.8 (7.3)	0.22
Mean SBP, mm Hg (SD)	142.2 (19.7)	144.3 (20.0)	0.41
Mean DBP, mm Hg (SD)	87.8 (12.2)	88.2 (11.6)	0.79
Antihypertensive medication (%)	51	48	0.52
Hypertension, %†	50	53	0.65
Current smoker, %	19	20	0.96
History of diabetes, %	15	16	0.97
Mean weekly alcohol consumption (SD)‡	6.6 (9.7)	5.5 (9.0)	0.37
Type of stroke, %§			0.65
Ischemic	73	77	
Hemorrhagic	11	8	
Transient ischemic attack	16	15	

SBP indicates systolic blood pressure; DBP, diastolic blood pressure.

*Comparison of active treatment and placebo groups based on χ^2 test for qualitative variables and Student's *t* test for quantitative variables.

†Systolic blood pressure ≥ 160 or diastolic blood pressure ≥ 90 mm Hg.

‡In number of standard drinks of alcohol.

§Qualifying (most recent) event for study entry.

the WMH-by-treatment interaction term to the above model and tested for its significance. Because the interaction term was significant, we performed stratified analysis by baseline severity of WMH. We also tested interaction between treatment and age, sex, center, and stroke type. Because distribution of WMH volumes is skewed, we used log-transformed WMH volumes to test for significance. All analyses were performed with SAS version 8.02 (SAS Institute Inc).

Results

Table 1 describes baseline characteristics by treatment allocation of all randomized study participants who had the 2 MRI examinations. The age of the study participants ranged from 35 to 85 years, and approximately 75% of them were men. At study entry, approximately half of the patients were taking antihypertensive medications, and 52% of the subjects had hypertension. There was no significant difference between the 2 treatment groups for age, gender, and vascular factors (Table 1). With regard to study regimen, 112 patients (58%) were given the combination of perindopril and indapamide (or their placebos), and 80 were given perindopril alone (or its placebo).

On baseline MRI, 42% of the patients had no WMH, 26% had mild WMH, 13% had moderate WMH, and 19% had severe WMH (Table 2). A stroke scar was visible at cerebral MRI in 55% of the patients. Among patients with a visible stroke scar, its size was small (<15 mm) in 41%, medium in 30%, and large in 29%. There were no significant differences for baseline cerebral MRI characteristics between placebo and active treatment groups. Factors associated with baseline severity of WMH for the entire sample are shown in Table 3. There was a significant trend for a relationship between

TABLE 2. Baseline MRI Characteristics by Treatment

	Placebo (n=103)	Active (n=89)	<i>P</i> *
Severity of WMH, %			0.21
None	38	47	
Mild	24	28	
Moderate	15	10	
Severe	23	15	
Stroke scar size, %			0.86
No scar	44	46	
Small	21	24	
Medium	18	16	
Large	18	15	

*Comparison of active treatment and placebo groups based on χ^2 test.

increasing age and severity of WMH. The prevalence of severe WMH was also associated with antihypertensive drug treatment at entry and with blood pressure level at randomization. Mean SBP was 13 mm Hg higher in the group of patients who had severe WMH than in those who had no WMH at entry (Table 3).

The second MRI was performed on average 36 months after baseline MRI (37 months in the placebo group, 36 months in the active treatment group; $P=0.10$). At the time of the second MRI, decreases in systolic and diastolic blood pressure levels compared with baseline measure were significantly larger in the treated group than in the placebo group. The mean decrease of systolic blood pressure was 12.5 mm Hg (SD=22.0) in the treated group compared with 1.3 mm Hg (SD=20.0) in the placebo group ($P=0.0004$), and

the mean decrease of diastolic blood pressure was 8.2 (SD=12.3) in the treated group compared with 3.9 (SD=15.5) in the placebo group ($P=0.04$). The proportion of patients who continued to take randomized therapy at the time of the second MRI was 79% in the active treatment group and 88% in the placebo group ($P=0.42$).

During follow-up, 24 patients developed new WMH, 16 (16%) in the placebo group and 8 (9%) in the active treatment group ($P=0.17$; Table 4). Overall, the total volume of new WMHs was 1.8 mm³ (SE=0.5). The mean (SE) volume of new WMHs increased with baseline grade of WMH, from 0.05 (0.8) for patients who had no WMH at baseline to 1.2 mm³ (1.2) for those who had a mild to moderate grade and 6.5 mm³ (2.0) for patients with a severe baseline grade of WMH. Other baseline variables were not associated with the total volume of new WMHs. The total volume of new WMHs was significantly lower in the active treatment group (mean=0.4 mm³, SE=0.8 mm³) compared with the placebo group (mean=2.0 mm³, SE=0.7 mm³; $P=0.012$; Table 4). We found a significant interaction between baseline severity of WMH and treatment allocation on the total volume of incident WMH ($P=0.001$). We therefore performed stratified analysis by severity of WMH at baseline and observed that the treatment effect on the total volume of new WMH was particularly marked in patients with severe WMH at baseline (Table 4). Further adjustments for height, stroke type, baseline blood pressure level, antihypertensive treatment intake, interval (in months) between the 2 MRI scans, and baseline severity of WMH gave similar results (Table 4).

Exclusion of subjects who had a stroke (n=20) during follow-up did not modify the pattern of results. We also performed separate analyses by study drug regimen (perindopril-indapamide combination and perindopril single-

TABLE 3. Factors Associated With WMH Grade at Baseline

	Baseline Grade of WMH				<i>P</i> *
	None (n=86)	Mild (n=53)	Moderate (n=26)	Severe (n=27)	
Mean age, y (SD)	55.9 (10.4)	59.7 (9.2)	61.1 (10.5)	65.5 (9.1)	0.0001
Male gender, %	80	76	69	85	0.49
Mean height, cm (SD)	170.6 (7.8)	168.4 (9.0)	168.2 (8.2)	170.1 (8.3)	0.37
Age at highest level of education, y (SD)	18	17	19	17	0.13
Mean SBP, mm Hg (SD)	136.0 (15.6)	144.6 (21.8)	146.6 (19.3)	149.3 (21.7)	0.003
Mean DBP, mm Hg (SD)	85.1 (10.8)	90.0 (13.4)	90.1 (10.8)	88.9 (12.9)	0.07
Antihypertensive medication, %	30	51	58	67	0.006
Current smoker, %	20	21	19	15	0.50
Diabetes, %	13	6	27	22	0.04
Mean weekly alcohol consumption, mean (SD)†	4.9 (7.3)	7.2 (9.6)	5.7 (7.4)	6.2 (9.4)	0.48
Type of stroke, %‡					0.64
Ischemic	44	27	15	14	
Hemorrhagic	50	20	5	25	
Transient ischemic attack	45	32	13	10	

SBP indicates systolic blood pressure; DBP, diastolic blood pressure.

**P* value from χ^2 test for qualitative variables and ANOVA for quantitative variables.

†In number of standard drinks of alcohol.

‡Qualifying (most recent) event for study entry.

TABLE 4. Presence and Volume of Incident WMH by Treatment

	Total (n=192)	Placebo (n=103)	Active (n=89)	P Value, Model 1*	P Value, Model 2†
Incident WMH, n (%)	24 (13)	16 (16)	8 (9)	0.17	0.10
Mean volume of incident WMH, mm ³ (SE)	1.8 (0.5)	2.0 (0.7)	0.4 (0.8)	0.012	0.009
Volume of incident WMH by initial grade of WMH, mm ³ (SE)					
No WMH	0.05 (0.8)	0	0.09 (0.8)	0.76	0.81
Mild to moderate WMH	1.2 (1.2)	1.3 (1.0)	0.9 (1.0)	0.58	0.71
Severe WMH	6.5 (2.0)	7.6 (1.0)	0	<0.0001	<0.0001

*P value generated from logistic regression for qualitative variables or from ANCOVA with adjustment for age, sex, and center.

†P value generated from logistic regression for qualitative variables or from ANCOVA with adjustment for age, sex, center, height, stroke type, baseline blood pressure levels, and antihypertensive treatment intake, interval (in number of months) between the 2 MRI scans, and baseline severity of WMH (if applicable).

drug therapy), and the results were similar in the 2 subgroups (data not shown). Interactions between treatment and sex ($P=0.83$), age ($P=0.47$), center ($P=0.96$), and stroke type ($P=0.55$) on the volume of WMH were not significant.

Discussion

In this placebo-controlled, double-blind trial of a blood pressure-lowering regimen that combined an ACE inhibitor (perindopril) and a diuretic (indapamide) in patients with a history of cerebrovascular disease, patients who received active treatment had a significantly lower total volume of incident WMH than patients who received placebo over 3 years of follow-up. The beneficial effect of this blood pressure-lowering regimen remained significant after adjustment for several variables, including age, gender, stroke type, baseline blood pressure, and severity of WMH at baseline. We also observed a 43% (95% CI -7% to 89%) risk reduction of the occurrence of new WMH in the active treatment group compared with the placebo group, although the difference did not reach statistical significance (8/89 [9.0%] versus 16/103 [15.5%], respectively; $P=0.17$).

WMHs are strongly associated with hypertension,^{5,19,25} and the results of some large observational cohort studies suggest that patients whose hypertension is better controlled have a more limited progression of WMH.^{5,25} The present study, the first to have implemented an MRI-based assessment of WMH in a randomized trial, confirms that it is possible to limit WMH progression with a perindopril-based blood pressure-lowering regimen in patients with cerebrovascular disease. A post hoc analysis also indicates that the greatest beneficial effect of antihypertensive therapy on WMH progression was observed in the group of patients who had severe WMH at entry. This result is consistent with previous studies showing that over time, patients with greater lesion volume at baseline have a greater increase in the number or total volume of WMHs.^{6,17,20,21,26}

The present findings must be considered in light of the limited power of the study. During the mean 3-year follow-up period, 24 of 192 patients developed new WMH, a ratio consistent with previous studies,²¹ but these relatively small numbers affect the power to detect the effect of treatment.

They also do not allow us to give precise estimates of the treatment effect on the incidence of WMH or the volume of incident WMH by regimen (perindopril alone or perindopril plus indapamide) or by stroke type.^{7,27} With regard to volume of WMH, we decided per protocol to measure only the volume of new WMH. Another option would be to also study the growth of baseline WMH, because it could participate in the overall increase in volume of WMH. Although the question addressed would be slightly different, this option should be considered in future studies to increase their power to detect a treatment effect. In our estimation of the volume of new WMH, we carefully excluded scars caused by stroke that occurred during follow-up, because the treatment effect for stroke could mask its effect on WMH. Furthermore, of the 20 patients who had a stroke during follow-up, only 2 had new WMHs, and exclusion of these patients from the analysis did not modify the results with regard to meaning and statistical significance. Selection of patients is a potential limitation of the present study, because those who agreed to participate in the MRI substudy were healthier than those who refused. This selection bias, which is usual in MRI studies, had no effect on the balanced distribution of the variables between the placebo and the active treatment arm. Furthermore, because the strongest treatment effect was seen in patients with the most severe grades of WMH at baseline, that is, in patients more likely to refuse than agree to participate, the selection bias observed is probably conservative. We therefore believe that this selection had no bearing on the validity of the present results, although it could have affected the study power.

Despite its limited power, our study has several strengths. Among the patients included in the selected centers, 87% (281/322) agreed to participate in the study, and among those who had their first MRI examination and who could participate, 93% (192/206) agreed to have a second MRI examination. Overall, despite deaths and patients who met exclusion criteria for MRI, the participation rate was 85% (192/225) between both examinations. The study is further strengthened by the methods used to estimate the volume of WMH. Limitations of visual scales to evaluate WMH severity, as well as WMH changes over time, have been discussed extensively.^{28–30} We used a semiautomated method to iden-

tify incident WMHs and to measure their volume. Special care was taken in standardizing the quality and reading conditions of the T2 scans acquired 3 years apart in the same patient. Finally, this substudy had the same favorable characteristics as the main PROGRESS study in terms of good adherence to treatment and maintained blood pressure difference throughout follow-up.

The selection of patients mentioned above limits our ability to extend the results of this substudy to all patients enrolled in the PROGRESS trial. The present study showed, in a particular subset of patients, that it is possible to limit the progression of WMH. These results now need to be confirmed and extended in further clinical trials, such as in hypertensive patients free of cerebrovascular disease. Our results could help design such future studies in terms of number of patients, duration of follow-up, stratification on baseline severity of WMH, and methods used to estimate the volume of WMH.

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Disclosures

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